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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Rima Kaddurah-Daouk *et al.*

Application No.: 09/687,575 Confirmation No.: 9336

Filed: October 13, 2000 Art Unit: 1625

For: COMPOSITIONS CONTAINING A COMBINATION OF A CREATINE COMPOUND AND A SECOND AGENT Examiner: N. Rahmani

MS RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF BELINDA TSAO NIVAGGIOLI, Ph.D.
UNDER 37 CFR §1.132

Dear Sir:

I, Belinda Tsao Nivaggioli, Ph.D., a citizen of Canada, residing in Atherton, California, hereby declare as follows:

1. I am presently the Chief Executive Officer of the Avicena Group, Inc. (Palo Alto, California). I have been working in the area of pharmaceuticals and nutraceuticals for approximately 14 years. A copy of my curriculum vitae is attached as Appendix A.

2. I have read the above-referenced application and presently pending claims 86, 91, 93, 95, 98-100, 133 and 135-140 (included herewith as Appendix B). It is my understanding that the invention is directed to methods of treating Parkinson's disease by administering a therapeutically effective amount of a combination of creatine, creatine phosphate, or a creatine compound and a neuroprotective agent.

3. In addition, I understand that claims 86, 91, 93-95, 98-100 and 133 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that "[A]pplicant has not guidance or

examples for treating Parkinson's disease using [a] pharmaceutical composition of creatine, creatine phosphate or a creatine compound and a neuroprotective agent."

4. The claimed invention is supported by the disclosure in the specification, in such a way as to enable one of ordinary skill in the art at the time the application was filed to practice the invention. The following examples shows how an ordinarily skilled artisan, at the time the application was filed, would have been able to use the methods described in the specification to determine that the compounds of the invention are effective in the disclosed MPTP model and then have been able to use the compounds of the invention to treat Parkinson's disease.

5. The effectivity of creatine on the MPTP mouse model of Parkinson's disease is accepted by the scientific community as evidence of the effectivity of creatine as a potential treatment of Parkinson's disease, as evidenced by the citation of this data on the National Institute of Health's website for the clinical trials of creatine for the treatment of Parkinson's (http://www.ninds.nih.gov/funding/research/parkinsonsweb /drug_summaries/creatine.htm). Currently, creatine is undergoing Phase III clinical trials.

According to the National Institute of Health website, creatine has demonstrated efficacy for prevention of MPTP-induced neuronal injury in rats (Exp Neurol. 1999;157:142-9; Pharmacol Rev. 2000;53:161-71.). Rats given a 1% creatine diet for 2 weeks experienced only a 10% loss of DA neurons after MPTP administration (not significantly different from non-MPTP treated animals) in contrast to a 70% neuronal loss among those not supplemented with creatine. Sparing of neurons in this model increased with higher levels of creatine supplementation, ranging from 0.25-1%.

6. Furthermore, the administration of creatine has been shown not to be futile for the treatment of humans in a double blind clinical trial of Parkinson's disease using both creatine and minocycline.

In this trial, eligible subjects were randomly assigned in a 1:1:1 fashion to receive 1) 10g/day of creatine monohydrate and placebo minocycline, 2) placebo creatine monohydrate and 200mg/day of minocycline, or 3) placebo creatine monohydrate and placebo minocycline. The primary futility analysis was at 12 months of follow-up, but each subject was followed for 18 months for additional safety information. Subjects and investigators were kept blinded to treatment group.

Subjects were men and women age 30 and over who had a diagnosis of Parkinson's disease but did not require medications for the management of their symptoms. Two of the three cardinal manifestations of Parkinson's disease (tremor, rigidity, and bradykinesia) were required; these findings had to be asymmetric. The diagnosis of Parkinson's disease must have been made within 5 years of randomization. Subjects were excluded if they had any secondary causes of parkinsonism, such as drug induced parkinsonism or structural lesions; had atypical parkinsonian syndromes; gait freezing or impairment in postural reflexes; had prior stereotaxis surgery for Parkinson's disease; used creatine, minocycline, or any investigational agent within 90 days prior to randomization; had known hypersensitivity to creatine or minocycline; used CoQ_{10} in doses greater than 300 mg 90 days prior to randomization; or had any clinically significant medical condition that could interfere with the subject's ability to safely participate in the study or be followed.

Creatine was administered as 5 g sachets mixed with 8 ounces of liquid taken twice a day and minocycline was administered as 100 mg capsules taken twice a day. Both were taken with meals.

The primary, prespecified outcome measure was the change in the total Unified PD Rating Scale (UPDRS) score from baseline to either the time at which there was sufficient disability to warrant symptomatic therapy for Parkinson's disease or 12 months, whichever came first. Disability was assessed by the sight investigator, based on impairment in ambulation, activities in daily living, and occupational status. The mean change in total UPDRS for each treatment group was compared to a prespecified futility threshold of a 30% reduction in the historically derived change in the total UPDRS, which was based on a placebo arm of a previous clinical trial. Tolerability was defined as the proportion of subjects taking study drug for the full 12 months. All severe adverse events (SAEs) were reviewed by the study medical monitor and an independent medical monitor. Both the site investigator and medical monitors assessed the potential relationship between SAEs, minocycline and creatine.

Subjects had a baseline medical history, physical examination, and underwent the UPDRS. Blood was obtained for serum chemistry and complete blood count. Participants were reevaluated at 1, 3, 6, 9, and 12 months (±6 days) after the baseline visit using the battery of clinical scales and blood was drawn again at 6 and 12 months.

Eligible subjects (200) were randomized to one of three treatment groups: Group I received creatine; Group 2 received minocycline; Group 3 received placebo. The

treatment groups were similar at baselines on demographic variables and total UPDRS and UPDRS subscores.

Compliance with study visits was high and only two patients in the creatine group and no patients in the minocycline group had missing values requiring imputation. The mean change (SD) in total UPDRS from either baseline to 12 months or the time at which symptomatic therapy was needed was 5.6 (8.69) for the creatine group and 7.09 (8.71) for the minocycline group (Table 1). The observed progression in both the creatine and minocycline groups did not exceed the predetermined futility threshold. Therefore, the null hypothesis that the means were less than or equal to the threshold value of 7.46 (30% less than the 10.65 DATATOP historical rate of progression) could not be rejected for creatine ($p = 0.96$) or minocycline ($p = 0.63$). Creatine and minocycline could not be rejected as futile using this analysis and therefore met the criteria for consideration of further clinical testing. Using multiple imputation instead of worst change score for the group to account for missing observations yielded similar results.

Table 1

Treatment group	**Mean (SD)**	**95% CI**
Primary Analysis*		
Total UPDRS		
Creatine	5.6 (8.69)	(3.48, 7.72)
Minocycline	7.09 (8.71)	(4.95, 9.23)
Placebo (Calibration)	8.39 (9.76)	(6.01, 10.8)
DATATOP Placebo/Tocopherol	10.65 (10.4)	(9.63, 11.67)

Worst change score for the group is used to impute missing values/

*Primary analysis compares each treatment group to the futility threshold, or 70% historical control, which equals 7.46.

The calibration placebo group mean change of 8.39 (9.76) fell outside the 95% CI for the DATATOP historical control of 9.63 to 11.67. The historical control was updated using the observed placebo information and the threshold value decreased to 7.2. Against this comparison, neither creatine ($p = 0.93$) nor minocycline ($p = 0.54$) could be rejected as futile. Additionally, an exploratory sensitivity analysis was performed based on the calibration placebo group. Using only data from the placebo group, the threshold value was recomputed as 30% less than 8.93 and the futility threshold decreased to 5.87. With a threshold of 5.87, neither creatine ($p = 0.6$) not minocycline ($p = 0.13$) could be rejected as futile, although minocycline was close to the prespecified alpha level of 0.10.

Combining all three arms of the study, 96 (48%) subjects required symptomatic therapy during the course of the trial. Subjects requiring symptomatic therapy had greater changes in their UPDRS scores than those who completed 12 months without the addition of symptomatic therapy. The 104 (52%) subjects who did not receive symptomatic therapy (or terminated prior to completion) had a mean change of 4.35 (8.83) on their total UPDRS score over 12 months compared to 12.36 (8.86) for the 22 subjects starting levodopa and 8.98 (8.84) for the 47 subjects starting dopamine agonists.

The effects of creatine on UPDRS progression were robust to the range of threshold values tested. Overall, the study showed that creatine slows down the progression of Parkinson's disease and can be used as a therapy for subjects with Parkinson's disease.

7. One of ordinary skill in the art at the time the application was filed would have been able to use the methods described in the specification to perform the claimed methods, e.g., administering creatine, creatine phosphate, or a creatine compound and a neuroprotective agent to treat Parkinson's disease. The specification clearly enables one of ordinary skill in the art to practice the invention.

9. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Belinda Tsao

Belinda Tsao Nivaggioli, Ph.D.

Feb 5, 2007
Date

Appendix A

Belinda Tsao Nivaggioli, Ph.D.
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WORK EXPERIENCE

The Avicena Group, Inc., Palo Alto, CA

Chief Executive Officer	1/05 - Present
Chief Operating Officer	12/01 – 1/05
Vice President of Operations	12/00 – 12/01
Director of Product Development	9/99 – 11/00

Avicena Group, Inc. (OTCBB: AVGO) is a late stage biotechnology company focused on developing products based on its proprietary understanding of the regulation of cellular energy processes. The company's core technologies, supported by a robust IP portfolio, have broad applications in both pharmaceuticals and dermaceuticals. Avicena's pharmaceutical program centers on rare neurological disorders (orphan diseases). The company is currently analyzing data from its Phase IIb/III trial in ALS (Amyotrophic Lateral Sclerosis, or Lou Gehrig's disease). Near term, Avicena intends to initiate a Phase III trial in Huntington's disease and a Phase III trial in Parkinson's disease. Avicena's science is well established and its products are safe and well tolerated. Unlike traditional biotechnology companies, Avicena's clinical programs are largely funded by government and non-profit organizations. Avicena presently derives revenue from the sale of proprietary ingredients to skin care manufacturers.

Oral-B Laboratories, A Gillette Company, Belmont, CA

Manager, Product Development, Floss and Interdental	11/98 – 9/99
Group Leader, Floss and Interdental	11/95 – 11/98

Development, scale up and manufacture of new interdental products, such as flosses and interdental devices. Involved in project management, procurement and setup of manufacturing line in the factory, market research, clinical studies, launch planning, preparation of sales materials and manufacturing logistics. Supervision of engineers and technicians.

The Gillette Company, Boston, MA
Research Scientist, Corporate Research and Development 11/94 - 11/95
Synthesis and microbiological assays of novel antimicrobial agents for treating plaque and gingivitis. Synthesis and studies of acidochromic materials. Worked closely with various business units to develop strategic business plans. Supervision of technicians and students.

Massachusetts Institute of Technology, Cambridge, MA 1993 - 1994
Postdoctoral Associate in Prof. Julius Rebek Jr.'s group. Studied chemical nucleases, self-replicating systems and combinatorial libraries. Collaborated with Prof. Alan Hatton, in the Department of Chemical Engineering in the study of water-soluble polymers using NMR and fluorescence spectroscopy.

EDUCATION

University of Toronto, Toronto, ON, Canada.
Ph.D. in Bioorganic Chemistry (January 1993). Study of conformation catalysis of decarboxylation by host-guest chemistry. University of Toronto Open Fellowship (1990 - 1992).

M.Sc. in Bioorganic/Physical Organic Chemistry (May 1990). University of Toronto Open Fellowship (1988 - 1990).

Oberlin College, Oberlin, OH, USA
A.B. (Hons) in Organic Chemistry (1988). Li Shu Fan Foundation Scholarship (1984 - 1988).

ASSOCIATIONS

Member of American Chemical Society (ACS), American Association for the Advancement of Science, the Society of Plastics Engineers, International Association of Dental Research

PUBLICATIONS / REFERENCES

Available upon request. As of March 1998, 5 papers were published in international journals, 6 presented at international conferences, 1 patent granted and 2 patent applications are pending.

LANGUAGES

English, Chinese and French (proficient in reading, writing and conversation).

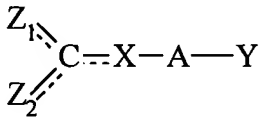
HONORED MEMBERS

Medicine's Who's Who 2004

APPENDIX B
Pending Claims
U.S.S.N. 10/695,265

86. A method for treating Parkinson's disease in a subject, comprising:

administering to a subject a therapeutically effective amount of a combination of creatine, a creatine phosphate or a creatine compound and a neuroprotective agent, such that Parkinson's disease in said subject is treated, wherein said neuroprotective agent is selected from the group consisting of inhibitors of glutamate excitotoxicity, 2,3 dimethoxy-5-methyl-6-decaprenyl benoquinone, nicotinamide, spin traps, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, N-acetylcysteine, antioxidants, lipoic acid, riboflavin, and CoQ10, wherein said creatine compound has the formula:



and pharmaceutically acceptable salts thereof, wherein:

a) Y is $-CO_2H$;

b) A is selected from the group consisting of: C, CH, C_1-C_5alkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, and C_1-C_5 alkoyl chain, each having 0-2 substituents which are selected independently from the group consisting of:

1) K, where K is selected from the group consisting of: C_1 -C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, and C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

2 -NH-M, wherein M is selected from the group consisting of: hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoyl, C_3-C_4 branched alkyl, C_3-C_4 branched alkenyl, and C_4 branched alkoyl;

c) X is NR_1, wherein R_1 is selected from the group consisting of:

1) hydrogen;

2) K where K is selected from the group consisting of: C_1-C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, and C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

d) Z_1 and Z_2 are chosen independently from the group consisting of: -NHR_2, wherein R_2 is selected from the group consisting of:

1) hydrogen;

2) K, where K is selected from the group consisting of: C_1-C_6 straight alkyl; C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_3-C_6 branched alkenyl, and C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3 a C_4-C_8 a-amino-carboxylic acid attached via the w-carbon; and

4 B, wherein B is selected from the group consisting of: -CO_2H, -NHOH, -SO_3H, and -NO_2, wherein B is optionally connected to the nitrogen via a linker selected from the group consisting of: C_1-C_2 alkyl, C_2 alkenyl, and C_1-C_2 alkoyl.

91. The method of claim 86, wherein said neuroprotective agent is a spin trap.

93. The method of claim 86, wherein said neuroprotective agent is carnitine.

95. The method of claim 86, wherein said neuroprotective agent is an antioxidant.

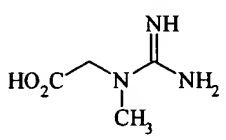
98. The method of claim 86, wherein said neuroprotective agent is riboflavin.

99. The method of claim 86, further comprising administering at least one additional neuroprotective agent or creatine compound.

100. The method of claim 86, wherein said creatine compound is creatine.

133. A method for treating Parkinson's disease in a subject, comprising:

administering to a subject a therapeutically effective amount of a combination of creatine, a creatine phosphate or a creatine compound and a neuroprotective agent, such that Parkinson's disease in said subject is treated, wherein said neuroprotective agent is selected from the group consisting of inhibitors of glutamate excitotoxicity, 2,3 dimethoxy-5-methyl-6-decaprenyl benoquinone, nicotinamide, spin traps, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, N-acetylcysteine, antioxidants, lipoic acid, riboflavin, and CoQ10, wherein said creatine compound is selected from the group consisting of: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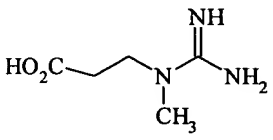
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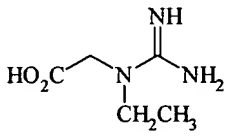
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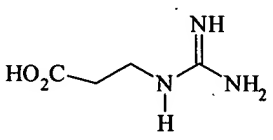
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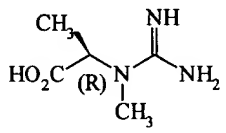
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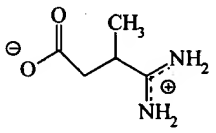
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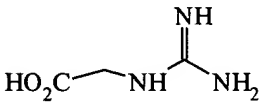
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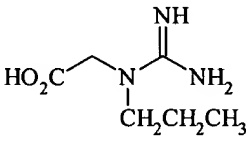
, and pharmaceutically acceptable salts thereof.

135. The method of claim 133, wherein said neuroprotective agent is a spin trap.

136. The method of claim 133, wherein said neuroprotective agent is carnitine.

137. The method of claim 133, wherein said neuroprotective agent is an antioxidant.

138. The method of claim 133, wherein said neuroprotective agent is riboflavin.

139. The method of claim 133, further comprising administering at least one additional neuroprotective agent or creatine compound.

140. The method of claim 133, wherein said creatine compound is creatine.